

(d) within approximately 15 minutes after contacting the liquid sample with the test strip, observing through the view window whether a line of color has appeared, indicating the presence in the test sample of the species, or serogroup of a species of bacteria, containing the crude carbohydrate antigen to which the purified antibodies are specific.

50. The method of claim 49 wherein the liquid sample is obtained from a human patient exhibiting clinical symptoms of a disease known to be caused by the bacteria species or serogroup of a species of which the crude antigen to be detected is characteristic.

Claims 35, 37-42, 44, 46-47, 51 and 52 are retained in unamended form.

Non-elected claims 1, 2 and 12-14 are retained pending possible filing of a divisional application.

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III. REMARKS

A. Drawings

A new set of drawings conforming to the rules is submitted herewith.

B. Priority

This section is not understood. Applicants' disclosure is not drawn to a method of detecting the presence of a carbohydrate antigen characteristic of at least one species or serogroup of a species of both gram-negative and Gram-positive bacteria; rather it is drawn to such a method for detecting the presence of a carbohydrate antigen characteristic of at least one species (for serogroup of a species) of either Gram-positive or Gram-negative bacteria.

Of the prior filed U.S. applications, Serial Numbers 09/139,720 and 09/458,988 teach a method for detecting carbohydrate antigens of Legionella bacteria, which are gram negative; Serial Number 09/397,110 and its parent application Serial Number 09/156,486

teach such a method for detecting a carbohydrate antigen of Gram positive bacteria. While Serial Number 09/139,720 does not suggest that the method it discloses be applied to detect Gram positive bacteria and Serial Numbers 09/156,486 (now abandoned) and 09/397,110 do not teach that the method they disclose should be applied to detecting Gram-negative bacteria, the method is itself the same for all practical purposes, and working with it led to the recognition that the method is applicable to the detection of carbohydrate antigens of both Gram -negative and Gram-positive bacteria. That broad generic conception is described in this application.

Applicant submits that there is no rule or requirement anywhere, that a continuation-in-part application of two or more prior applications can only be so designated if they all express the same underlying generic concept.

Moreover, generic concepts often grow from experience in working with several species, and when that happens, it is orderly and logical to rely on applications disclosing earlier, narrower concepts which led up to a generic concept, while recognizing that each earlier, narrower application discloses only a part of what is a later application disclosing a more generic concept.

The common denominator among all of the applications here is the detection of a carbohydrate antigen indigenous to a species, or serogroup of a species, of bacteria. The recognition here, which emerged from work done with particular individual carbohydrate antigens from various bacteria species or their serogroups that one method can be applied to attain the goal of rendering each of such carbohydrate antigens readily detectable was arrived at by a core group in essence, of the same researchers.

It is simply not understood what is improper about claiming the priority of earlier

applications for what they disclose, notwithstanding that this one is the first application to describe a generic concept applicable to indigenous bacterial carbohydrate antigens in general.

Accordingly, it is requested that the suggestion, albeit somewhat veiled that the priority of at least 09//156,486, 09/397,110 and 09/139,720 cannot be relied on for the segments of the generic concept that they each represent either be supported by citation of a rule, statute or authoritative decision supporting it or that it be withdrawn.

C. Specification

Applicants submit herewith a new Abstract which conforms to the requirement quoted in the action, paragraph 4.

The Examiner's position regarding incorporation by reference is not understood. The M.P.E.P. § 608.01 (p) 1 is understood to encourage incorporation by reference of material contained in earlier filed, pending U.S. patent applications. The Examiner's apparent position that documents incorporated by reference must be published before the incorporation is made is not supported by the cited M.P.E.P. section. If the Examiner persists in limiting incorporation by reference to published documents, Applicants request the Examiner to explain why the Manual is not being followed

Applicants point out that Application Serial Number 07/706,639 which was not incorporated by reference herein, but is cited to illustrate the preferred immunochromatographic devices used in the preferred assays, has issued and its patent number has been incorporated into the application by this amendment.

It is noted that in the further discussion of "Incorporation by Reference" at pp 15-16

of the action the Examiner cites three In re Hawkins cases which the M.P.E.P. relies on to show that incorporation "by reference of essential material by reference to a foreign application or patent, or to a [non-patent] publication" is improper. See MPEP 608.01 (p) A 2., August 2001 ed., page 6000-80. This is in stark contrast to the M.P.E.P. 608.01 (p) A 1., specific statement in the same edition, page 600-79 that "An application for patent may incorporate 'essential material' by reference to (1) a U.S. patent, (2) a U.S. patent application, or (3) a pending U.S. application, subject to the conditions set forth below" (Emphasis added) None of these conditions requires that material contained in another copending commonly assigned U.S. patent application must be physically transferred into the present specification because it is "essential"-- all indications are to the contrary.

Applicant's counsel emphasizes in this regard, that if the Examiner can resolve the apparent contradiction between her apparent position and what the M.P.E.P. says, so that the position does not appear to be asserted merely to impose undue burden, harassment and unnecessary expense upon Applicants, in derogation of the M.P.E.P., steps will be taken to arrive at consensus about what it is that the Examiner wants "physically incorporated"

The inadvertent misstatement in the specification (Office Action, numbered paragraph 6) that Legionella is "Gram-positive" has been corrected by this amendment.

D. Claim Objections

The inadvertent typographical error in Claim 22 (Office Action, par.7) with respect to the word "serogroup" has been rectified by this amendment. In addition, part(e) of Claim 22 has been changed to recite "by contacting" instead of "by contact of".

Claim 43 has been amended to delete the word "Legionella" in response to par.8 of Office Action, so that Claims 45 and 46 no longer broaden the scope of the broad claim

from which they depend.

The office action's statement (par.9) about claim numbering is not understood. Applicants have not "renumbered" the claims when some claims were cancelled. To the contrary, Claims 3-11 and 15-21 were cancelled in the response filed March 11, 2002 and new claims 22-52 were added, all of which accords with 37 C.F.R.1.126. The inadvertent typographical error which resulted in the presence of two claims "43" is regretted, and the Examiner's courtesy in correctly numbering the first one as "42" is appreciated.

The withdrawal of certain prior rejections (Office Action par. 10) is noted with appreciation.

E. Response to Claim Rejections -35 U.S.C. § 112

The rejection of Claims 22-52 under 35 U.S.C. § 112 as nonenabled is traversed. This rejection appears to be based upon the document fragment, "Critical Synergy, The Biotechnology Industry and Intellectual Property Committee of the Biotechnology Industry Organization at the October 17, 1994 Hearing of the U.S. Patent and Trademark Office, San Diego, CA" pages 100-107 cited at 7-8 of the Office Action. Applicant's counsel has endeavored for many months to obtain a copy of this entire "publication", because the fragment cited in the Action and made available to such counsel by the Examiner is clearly taken out of context, geared to specific technology areas that are non-inclusive of the area of immunoassays, antigens and antibodies with which the application is concerned, where standards of disclosure and of level of skill in the art have been developing since at least the 1960's. This area is unlike gene identification and protein purification to extremely high degrees of purity, which seem to be the major topics of the fragment. Moreover, the fragment is presented from a strongly partisan viewpoint but the identity or identities of the

speaker(s) is concealed.

In the immunoassay and antigen -antibody area, persons of ordinary skill in the art have a large body of knowledge concerning equivalence of certain reagents, lyophilization techniques, the interchangeability of centrifugation, allowing a mixture to settle naturally and then decanting, or aspirating off an upper layer and (3) other common laboratory techniques that separate layers of two liquids, these being a few of the ordinary items listed in the Office Action as so esoteric that infinite detail is needed.

The sudden comparison in the Action of these and other commonly understood aspects of immunoassay, including antigen-antibody work to what may (or may not, given the apparent bias of the unknown writer(s) of the Critical Synergy fragment), be still under exploration in intensive protein purification and/or gene identification is apparently intended to impose upon those in the immunoassay (including antigen-antibody) field, an unprecedentedly high standard of disclosure of infinite detail that then imposes an equally restrictive amount of detail upon claim terms, all accomplished without any change in the level of disclosure or claiming accepted by others in the examining corps. Doing this without advance warning that standards are to be changed and made more restrictive than ever before, and opportunity for public discussion followed by rule-making is inconsistent with due process of law and totally unfair to applicants accustomed to greater understanding of the level of ordinary skill in their own particular field of endeavor.

The Examiner's reliance on the Synergy fragment supplied is particularly questionable as a matter of law, moreover, when the following facts are considered:

1. Initial inquiry for this entire document at the Biotechnology Industry Organization which, according to the office action, "published" the whole of the cited document,

elicited the information that the document is unavailable because "it's too old".

Further searching inquiry over several phone calls and by 2 or 3 different people established that the alleged "publisher" has no copy, cannot identify anyone else who does and doesn't consider that it has any responsibility for assisting anyone to find it.

2. Efforts were made to find the whole document by inquiries to each of the following, all of whom stated they had no copy and some of whom said "it's not published" or "there's no such publication", after looking for it and finding no record of any sort regarding it:

1. Patent Depository Library, San Diego, CA
2. U.S. Department of Commerce Library
3. Patent and trademark Office libraries and offices as follows:
 - a) Biotechnology Library
 - b) Scientific and Technical Information Center
 - c) Office of the Solicitor
 - d) Patent and Trademark Office Library
4. Library of Congress
5. U.S. Senate Library
6. Canada Institute of Science & Technology
7. National Library of Medicine
8. LEXIS
9. Westlaw
10. British Library

11. Georgetown University Law Library

12. Federal Depository Library

13. Linda Hall Library of Science, Engineering and Technology

We emphasize that this investigation did not merely involve failure to find it on a library shelf; or even find it in a library catalogue, but involved direct communication with knowledgeable personnel who made what they represented to be serious efforts to locate such a "publication".

From all of this, it can only be concluded that, whatever the motive or inspiration for reliance on this out of context fragment from a purported whole document of 107 pages may be, it is misplaced and the fragment should be laid to rest in the same way that the apparent original sponsor, the Biotechnology Industry Organization, has already fully buried it.

The rejection of Claims 22-52 on the apparent ground that one skilled in the art of antigen-antibody immunology techniques would be incapable of practicing it because the first step involves culturing a bacterial species or serotype of a species and it continues through obtaining an essentially protein-free carbohydrate antigen, coupling the antigen to a column through a spacer molecule, passing antibodies over the column and then utilizing the resultant antigen-specific antibodies in an assay to detect the crude carbohydrate antigen is based upon an assumption that is not completely clear, but seems to suggest this would need to be done in one experiment rather than step-by-step over a time period if it were to be a proper method under 35 U.S.C. §101. If this is the premise of the rejection at pp.5-6 Of the action, the Examiner is requested to point out an authority that so holds. If it is not the premise, then further clarification is requested.

The art of purification is said in the action to be "highly unpredictable" at p. 6 of the

action; upon what authority is it stated that the art of purifying a bacteria carbohydrate antigen to the point that it contains no more than 10% protein is unpredictable? Is there a factual basis for the statement? If so, what is it?

What is the need or other reason for placing the various method steps(which were separated into labeled examples for clarity and ease of location of specific steps in the specification) in one "hybrid method" example? What does this have to do with the patentability of the method?

The methodology described, exemplified and claimed in Serial Numbers 09/139,720, 09/397,110 and its parent application and in this application is basically the same method; it applies whether the bacteria is Gram-negative or Gram-positive so long as the bacteria species or serogroup contains at least one characteristic carbohydrate antigen- it is unclear what the Office Action means when it states" there appears to be no conception of a method for detecting the presence of a carbohydrate antigen characteristic of at least one species of serogroup of a species of bacteria--i.e., both gram negative and gram positive bacteria in one method using one purification procedure for any type of bacteria" The specification describes one general method which is subject to many variations, for obtaining a carbohydrate antigen containing not more than 10% protein from any type of bacteria. It does not describe a method for detecting a carbohydrate antigen characteristic of both a gram negative and a gram positive bacteria species or serotype thereof at the same time. The application does not suggest that a carbohydrate antigen characteristic of both a gram-negative and a gram-positive bacteria exists, nor does it describe or claim an assay wherein each of a gram positive and a gram negative antigen are being targeted simultaneously(though such an assay is certainly possible). The purport of the quoted

statement, in short, is ambiguous and is not understood.

There is a teaching exemplifying a wet cell pellet in the specification, contrary to p. 6 and p. 12 of the action. It appears not only in the material incorporated by reference from Applications Serial Numbers 139,720, 156,486 and 397,110 but specifically in Example 2 at pp.14-15 wherein broth supernatant from a bacterial culture is treated with cetyl-triammonium bromide in an ice bath with stirring, allowed to stand overnight and centrifuged to give a "pellet"--which those of ordinary skill in the art will readily understand to be a "wet cell pellet"-- and a supernatant.

Another such wet cell pellet is described as obtained from the supernatant in numbered procedure (2) on page 15.

In addition, the specification discloses and exemplifies separating mixtures into two layers (liquid-liquid or liquid-solid) by centrifuging, and by allowing settling of a heavier material from lighter material by allowing a mixture to stand overnight throughout Example 2 on page 15. Methods of removing an upper liquid layer are obvious and well-known and normally are matters of choice having no effect upon results; they including decanting, filtering(when one layer is solid), and aspiration of an upper liquid layer.

It is pointed out, however, that this specification teaches that

"Many methods for effecting these separation and purification steps are known in the literature and may be substituted for those herein described without departing from the scope of this invention, so long as the purified antigen is essentially protein-free as herein described" (p.14)

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"The principles of this invention... lend themselves readily to a plethora of adaptations of permutations of and combinations with assay techniques previously reported by others. Many of the steps disclosed herein can be accomplished using different reagents or conditions from those specifically disclosed. Other methods of purifying carbohydrate antigens to an essentially protein-free state can readily be devised." (p.25)

In short, it is clear that Applicants do not contend any antigen purification method, as discussed herein, to be an essential part of the invention disclosed, rather, what is critical to the attainment of a successful assay is that the carbohydrate antigen contained and used to purify antibodies employed in the assay contain not more than about 10% protein.

The office action, p. 8, overlooks that Applicants have taught all the critical steps to achieving the desired assay results and that this is what § 112 requires. The office action at this page also overlooks that specific examples, including that of Example 5c, p. 20 are only specific embodiments of work that has been done and do not at all purport to lay down requirements unless the overall disclosure teaches a particular criticality. Apropos of the composed of Reagent A-Tween 20 containing 0.05 % sodium azide and 0.5 % sodium dodecyl sulfate in a 0.05 M sodium citrate-sodium phosphate buffer of pH 6.5, this is a nearly neutral pH buffer solution found to promote chromatographic flow. It is not required "to produce the crude carbohydrate antigen" as alleged by the Examiner at p. 8. As the specification points out on p. 21 under "Results of Sample Testing" the samples used were

urine samples which are well known in the art to open up dead bacteria so that their antigenic components are accessible in assay procedures. Urine, in general, is known to have a far more pronounced effect on breaking open cell walls of bacteria than any nearly neutral pH6.5 buffer could possibly exert. Moreover, in the case of Example 5 C and D employing urine as the sample necessarily makes bacteria therein subject to its influence for a far longer time than the urine sample containing dead bacteria and also target antigens from the bacteria that have already been released from its cell wall material, is contacted with Reagent A. If anything, Reagent A as described at p. 20 of the specification, at most may tend to dilute the effects of urine itself on bacterial cell walls rather than enhance it.

As to the Examiner's comment at the top of page 9, Applicants' assignee employs many different "Reagent A" type buffers in its assays. In general, none of them has any critical effect on assay outcome except when a buffer is specially formulated for a particular purpose other than promoting flow. When that is the case, the specification so states, as it does relative to the buffer that has a special purpose in Serial Number 09/458,998.

F. Claim Amendments and Objections

On p. 9 of the action, the Examiner criticizes Claim 24 for its recitation that the bacteria initially cultured contain a crude antigen sought to be detected in the assay of step(e) that "is a lipo-teichoic acid, a teichoic acid, or a derivative of either" and says the specification "fails to disclose the production of derivatives" The statement is unclear because when the bacteria possess a characteristic antigen that is a derivative of teichoic acid or lipo-teichoic acid, that derivative is not "produced", it is a component of the bacteria in its natural state. If antibodies are raised to it in the well-known manner set forth at p. 13, first paragraph of the specification, and they are purified according to this invention they can

be used in the preferred ICT assay of this invention, to detect the crude antigen which is a derivative of teichoic acid or lipo-teichoic acid. There is nothing mysterious about any of this and the last paragraph of the action, p. 9, is accordingly not understood. The specification clearly discloses (1) at p. 9 that the invention is directed to detecting "bacterial carbohydrate antigens of all types including...antigenic lipo-teichoic acid and teichoic acids and their antigenic derivatives" and (2) at p. 12 where it is noted that the invention offers "unique capabilities in regard to ready diagnoses of bacterial infections caused by any bacterium with one or more carbohydrate antigens of the types already mentioned--i.e....antigens comprising lipo-teichoic acids or teichoic acids and derivatives of either" Moreover, inasmuch as esters are the most obvious and well-known derivative of acids, those of ordinary skill in the art would readily be able to raise antibodies to antigens comprising esters of lipo-teichoic acid or teichoic acid and to purify the antibodies according to this invention and detect them in the preferred ICT method described, contrary to the contentions advanced at p. 11 of the action. The Examiner's comments regarding "derivatives" at p. 9 of the action and "esters" at p. 11 of the action are fanciful and have no supporting documentation. Absent a clear teaching in a reference of a problem that can be pointed out, these rejections should be withdrawn.

The Examiner's references to "free protein carbohydrates" is ambiguous and is not understood. The preferred procedures of Application 09/139,720 are exemplary, but a limiting upon this application.

As to the point raised in the paragraph bridging pages 11 and 12 of the specification, the specification teaches that any culture methods, including any of those already known for culturing bacteria, and any method for obtaining carbohydrate antigens that contain no more

than about 10 % protein, including any of those heretofore known can be used. There is a wealth of such known material and there is nothing cited by the Examiner that suggests the great problems the Office Action postulates at pages 11-12:

The claims herein have been amended to more particularly and clearly define the present invention. It is noted, however, that the rejection of par. 12, pp. 12-13, has already been shown to have no foundation in important respects and has , accordingly not been used as a model for claim amendments. However, Claim 22 has been extensively rewritten to accord more completely with this invention. A separate Exhibit A appended hereto shows the portions added to this and other claims by underlining them and the portions deleted by enclosing them in brackets.

G. Double Patenting

Applicants believe the amendments to the present claims go far to aid in demarcating them from claims of the identified co-pending applications. Applicants also note that , to the extent it may be needed, Applicants are willing to supply appropriate terminal disclaimers to insure that this application and one or more co-pending applications contain claims that have the same expiration date where claims overlap, but note that the need for this cannot be knowledgeably evaluated until claims are allowed in this and co-pending applications.

H. 35 U.S.C. § 103 Rejection

The rejection based upon Imrich et al in view of Barthe is without merit. Imrich et al, as the Examiner indeed acknowledges, is not concerned with and does teach assays which detect bacterial carbohydrate antigens. It furthermore presents no evidence that its device was ever actually utilized to detect either Legionella pneumophila or Haemophilus influenza

of any type.

Barthe et al discusses, inter alia, a monoclonal antibody which "recognized an epitome common to all tested serogroups of Legionella pneumophila and attached to the major constituent of the outer membrane" (Abstract, p. 1016). Applicants' antibodies to Legionella pneumophila Serogroup 1, purified as described in detail in Application Serial Number 09/139,720 does not recognize any epitope present on lipopolysaccharide from all of Serogroups 1-8, and instead manifests specificity toward an epitope of the serogroup 1 antigen. Applicants' antibodies to Legionella pneumophila Serogroup 1 as used in Applicants' ICT tests have the practical utility, undemonstrated by either Imrich or Barthe et al, that they capably, rapidly and reproducibly recognize Legionella pneumophila serogroup 1 in a manner that enables ready differentiation of Legionnaires disease caused by that organism from other respiratory diseases with highly similar overt clinical symptoms. No such advantage can be claimed from the cumbersome methodology disclosed by Barthe and there is nothing whatever to suggest, logically, that combining Barthe's monclonal antibody with Imrich's method or device would produce the advantages that Applicants' commercially available ICT Legionella pneumophila serogroup 1 test affords to the medical community. The Examiner's generalizations from cases cited in par. 23 of the action do violence to the facts of the cases and in no sense render either Applicants generic invention presented here, or the specific invention described in Application 09/139,720 "obvious to one of ordinary skill in the art as of the time invention was made."

CONCLUSION

The rejections in the June 3, 2002 office action are lacking in merit and should be

withdrawn. Early action to that effect is courteously requested.

Respectfully submitted,

A handwritten signature in cursive script, reading "Mary Helen Sears". The signature is written in black ink and is positioned above the printed contact information.

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